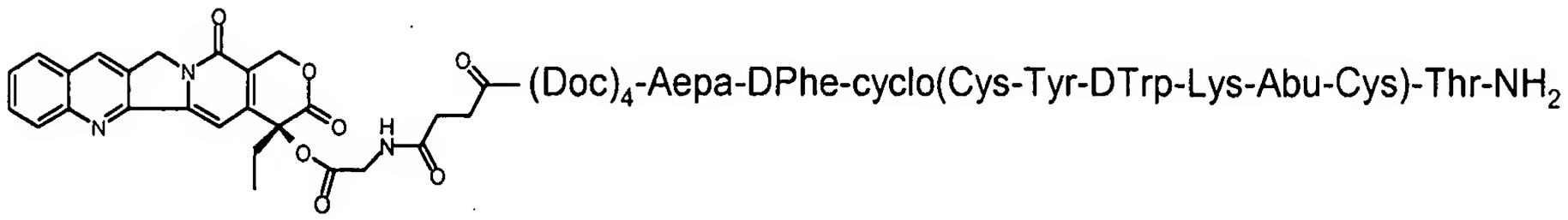
REMARKS

In the instant Action, claims 1-18 and 20-25 are listed as pending, and the Examiner has required restriction/election with respect to the following inventions or groups of inventions which are allegedly not so linked as to form a single general inventive concept under PCT Rule 13.1:

- Group I: claims 1-17 and 20, drawn to compounds of the formula $X\text{-}B^1\text{-}B^2\text{-}B^3\text{-}B^4\text{-}Z$ and pharmaceutical compositions thereof.
- Groups II-XXXIV: claim 18, drawn to precursor compounds useful as intermediates in chemical synthesis, where each compound recited is a separate invention.
- Groups XXXV-XLVII, claims 21 and 22, drawn to methods of treating diseases, where each disease: fibrosis, benign prostatic hyperplasia, atherosclerosis, restenosis, breast cancer, colon cancer, pancreas cancer, prostate cancer, lung cancer, small cell ung carcinoma, ovarian cancer, epidermal cancer, and hematopoietic cancer, is a separate invention.

The Examiner further allges that claims 23-25 link inventions XXXV-XLVII, and states, at page 2 of the instant Action, that "[t]he restriction requirement between the linked inventions is **subject to** the nonallowance of the linking claim(s), claims 23, 24 or 25, with respect to the receptor type – somatostatin, bombesin or LHRH type and its association with each disease."

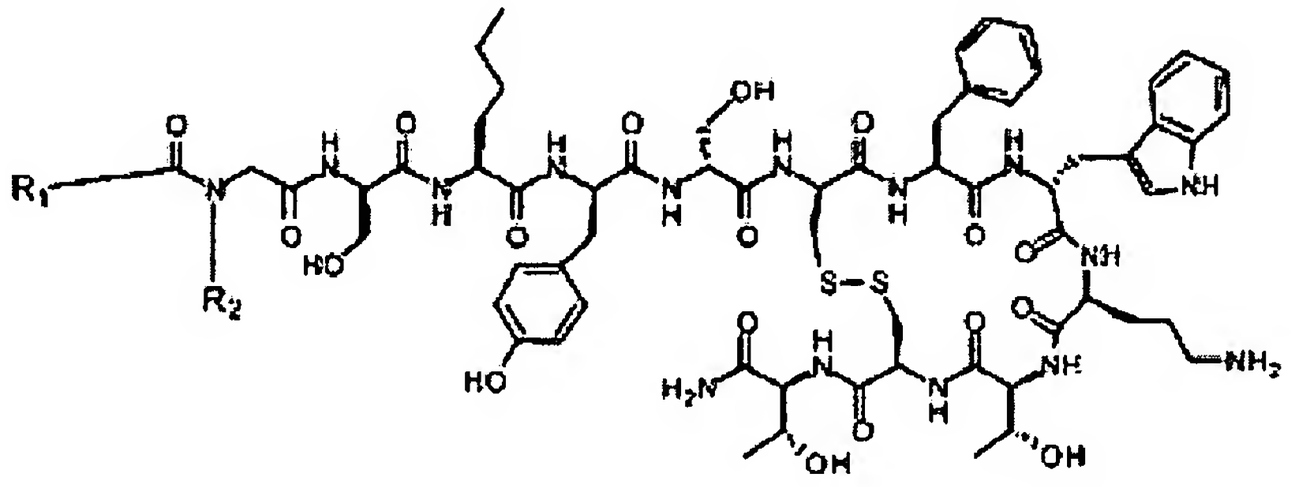
Applicants hereby elect Group I for examination, ***with traverse***. Applicants further tentatively elect the compound of Example 22, *i.e.*,

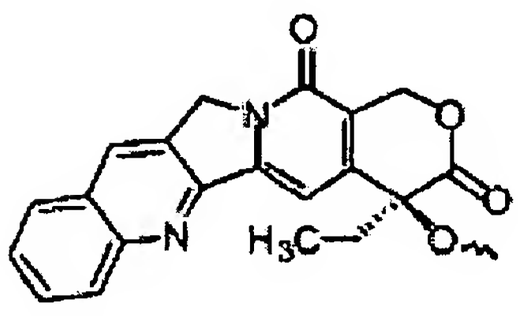
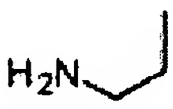
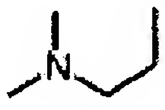
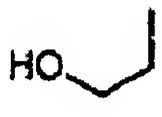
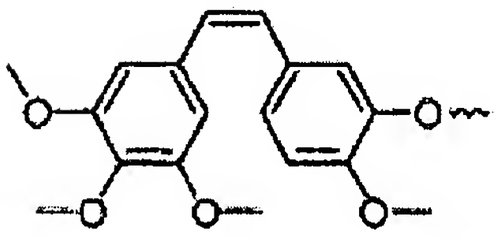
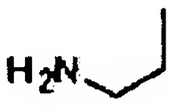


as Applicants' species within Group I. Claims 1, 2, 5, 6, 9, 10, 13, 14, 15, 17, and 20-25 encompass the elected invention.

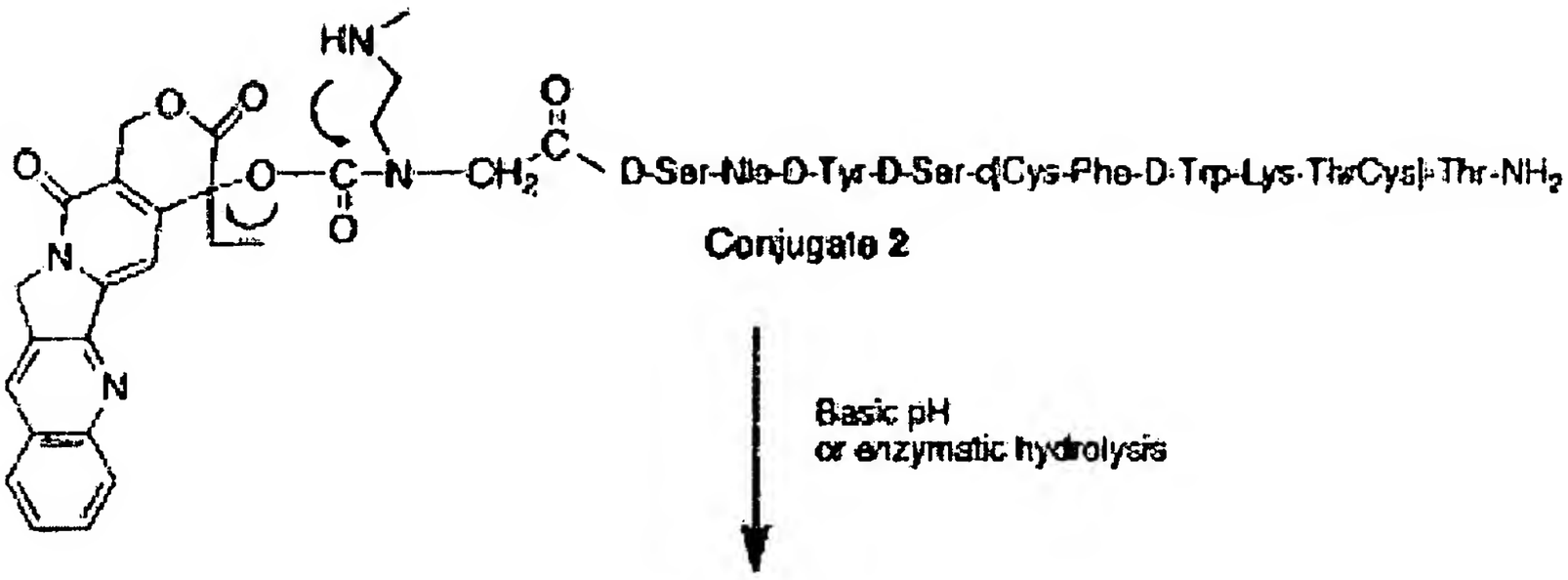
The Examiner alleges, at page 3 of the instant Action, that "FUSELIER … teaches camptotheoin [sic] conjugates through BINAR linking groups to somatostatin analogs PENTETREOTIDE. Fuselier teaches that conjugate 2 was administered to nude mice bearing NCI-H69 transplanted small cell lung carcinomas (page 802)." The precise structure of "conjugate 2" can be ascertained from Table 1 shown at page 801 of the Fuselier paper, as reproduced below:

Table 1. Structures of camptothecin and combretastatin conjugates containing various BINAR linking groups

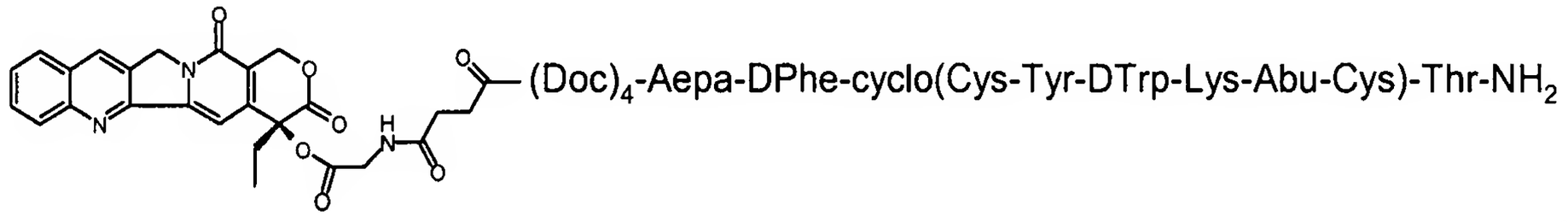


R_1	R_2	Compd
		1
		2
		3
		4
		5
		6

Further, the Abstract of the Fuselier paper states "Here, we describe a new **carbamate** linker system containing a series of built-in nucleophile assisted releasing (BINAR) groups which enable the 'fine-tuning' of intracellular cleavage rates of free cytotoxic agents containing reactive OH groups." (emphasis added). "Conjugate 2" itself, as shown in Figure 1 at page 800 of the Fuselier paper, is reproduced below which clearly shows the precise structure of the "new **carbamate** linker system":



However, Applicants respectfully submit that the claimed invention of the instant application does not have such **carbamate** linker system. For example, the tentatively elected compound of Example 22, *i.e.*,



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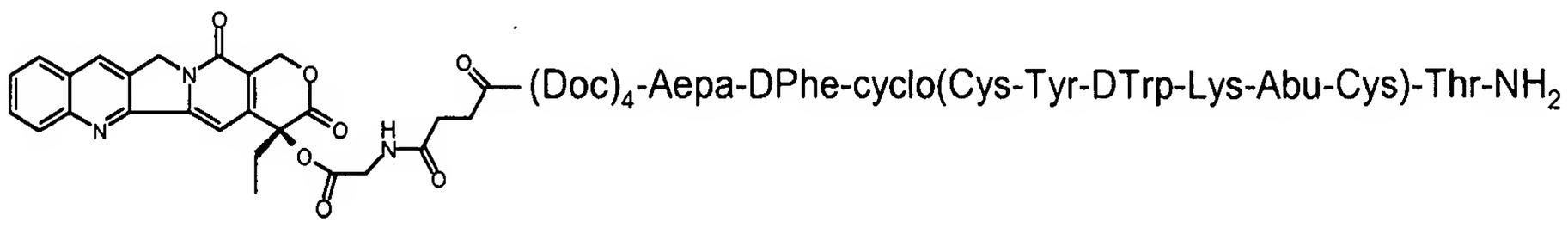
clearly does not have the specific **carbamate** linker system as disclosed in the Fuselier paper. Should the Examiner not be convinced by Applicants' showing that the claimed invention of the instant application does not encompass the specific **carbamate** linker system as disclosed in the Fuselier paper, Applicants respectfully request that the Examiner to show, for example, how claim 1 of the instant application encompasses the specific **carbamate** linker system as disclosed in the Fuselier paper. Absent such a showing by the Examiner, Applicants respectfully request reconsideration and withdrawal of the unity of invention objection over the Fuselier paper.

The Examiner alleges, at page 3 of the instant Action, that "WO 97/19954 A1 ... teaches doxorubicin, and anthracycline compounds conjugated to an LHRH analog, a somatostatin analog, or a bombesin analog through a -C(O)-alkyl-C(O)- linker moiety and pharmaceutical compositions (claims 1-32) and a method of treating cancer (and the use of the compounds in treating tumors) via administration of said compounds (claims 33-36)." However, claim 1 of the instant application requires that "when X is doxorubicin or a doxorubicin derivative, at least one of m [as in $(Doc)_m$] and n [as in $(Aepa)_n$] is not 0", whereas claims 1-32 of WO 97/19954 A1 do not contain the Doc nor Aepa moiety at all. That is, the only linker system disclosed in WO 97/19954 A1 is a -C(O)-alkyl-C(O)- linker moiety. In view of this clear showing that the claimed invention of the instant application requires the presence of at least one of

Doc and Aepa when X is doxorubicin or a doxorubicin derivative, whereas WO 97/19954 A1 only teaches a -C(O)-alkyl-C(O)- linker moiety, Applicants respectfully request reconsideration and withdrawal of the unity of invention objection over WO 97/19954 A1.

Next, the Examiner alleges, at page 5 of the instant Action, that the compounds of the instant application fail to satisfy Annex B, Part I(f) of the Administrative Instructions under PCT which states that, "wherein a single claim defines alternatives (chemical or non-chemical) ... the requirement of a technical interrelationship and the same or corresponding special technical features as defined in Rule 13.2, shall be considered to be met when the alternatives are of a smilar nature." The Examiner alleges, at page 5 of the instant Action, that "the compounds fail to satisfy requirement (A) [of Annex B, Part I(f) of the Administrative Instructions under PCT], as they are targeted toward three different receptors – somatostatin, bombesin and LHRH, thus the compounds do not have the same activity/function. ... The independent claim recites no structure, and dependent claims recite only structure of one of the various components independent of other components of the dcompound, thus failing to meet the requirement of (B)(1) [of Annex B, Part I(f) of the Administrative Instructions under PCT]."

In reply to this criticism, Applicants respectfully point out that claim 1 of the instant application is directed to a novel targeted cytotoxic or cytostatic compound having the unique and inventive linker structural system which is specifically defined therein and which is not taught, suggested or otherwise disclosed in the Fuselier paper nor WO 97/19954 A1 as discussed in detail above. The fact that claim 1 generically recites "a cytotoxic or cytostatic agent" or that claim 1 generically recites "a ligand of a biological receptor" does not detract from the essence of the claimed invention which is the unique linker system which serves as the same or corresponding special technical feature as defined in Rule 13.2. To illustrate this point, the tentatively elected compound of Example 22, *i.e.*,



has the unique linker system comprising rvGly-Suc-$(Doc)_4$-Aepa, which renders this cytotoxic compound novel and inventive over, *e.g.*, the Fuselier paper nor WO 97/19954 A1 as discussed in detail above, irrespective of the fact that the camptothetin moiety itself may already be known and even if the somatostatin moiety is already known in the art. In view threof, Applicants respectfully request reconsideration and withdrawal of this objection.

Consideration and allowance of all pending claims are respectfully requested.

Examiner Kosar is invited to telephone Applicants' undersigned attorney to facilitate prosecution of this application, if deemed necessary.

Respectfully submitted,

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